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REVIEW ARTICLE

Mucosal Healing in Ulcerative Colitis: A Comprehensive Review

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Abstract Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by periods of remission and periods of relapse. Patients often present with symptoms such as rectal bleeding, diarrhea and weight loss, and may require hospitalization and even colectomy. Long-term complications of UC include decreased quality of life and productivity and an increased risk of colorectal cancer. Mucosal healing (MH) has gained progressive importance in the management of UC patients. In this article, we review the endoscopic findings that define both mucosal injury and MH, and the strengths and limitations of the scoring systems currently available in clinical practice. The basic mechanisms behind colonic injury and MH are covered, highlighting the pathways through which different drugs exert their effect towards reducing inflammation and promoting epithelial repair. A comprehensive review of the evidence for approved drugs for UC to achieve and maintain MH is provided, including a section on the pharmacokinetics of anti-tumor necrosis factor (TNF)-α drugs. Currently approved drugs with proven efficacy in achieving MH in UC include salicylates, corticosteroids (induction only), calcineurin inhibitors (induction only), thiopurines, vedolizumab and anti-TNFα drugs (infliximab, adalimumab, and golimumab). MH is of crucial relevance in the outcomes of UC, resulting in lower incidences of clinical relapse, the need for hospitalization and surgery, as well as reduced rates of dysplasia and colorectal cancer. Finally, we present recent evidence towards the need for a more strict definition of complete MH as the preferred endpoint for UC patients, using a combination of both endoscopic and histological findings.

Key Points

Mucosal healing (MH) is currently considered a crucial endpoint in the management of ulcerative colitis patients.

Through strikingly different pathways and mechanisms, most drugs currently approved for UC are able to both induce and maintain MH in the majority of patients, but anti-tumor necrosis factor-α agents have shown superior results in moderate to severe disease.

Recent evidence highlights the importance of complete MH, corresponding to normal mucosa during endoscopic examination, when aiming for improved outcomes in UC.

1 Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD), first named in 1859 by Samuel Wilks [1]. More than 150 years later, its origin is still unknown, and most likely results from the interaction between various genetic and environmental factors [2]. It is currently defined by a continuous mucosal inflammation of the

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rectum and a variable extent of the colon, without granulomas on mucosal biopsies [1].

UC is a lifelong disease, characterized by periods of remission and periods of relapse—the latter, often presenting with a combination of diarrhea, rectal bleeding, abdominal pain, malaise and weight loss, is responsible for the overwhelming majority of the disease burden and diminished quality of life [3, 4]. Patients newly diagnosed with UC have a 5-year risk of colectomy of 10–35% [5], and ultimately, persistent and extensive inflammatory activity increases the long-term risk of colorectal cancer [5].

In the past, disease management was aimed at controlling symptoms, such as rectal bleeding and increased frequency of bowel movements [3]. Symptom assessment remains an important facet of UC approach because it is easily employed in the clinical setting [4], is widely accepted by patients and physicians alike, and is still the decisive factor when considering the severity of the disease, requirement for hospital admission, and indication for surgery [3]. The adoption of standardized clinical scores, such as the Truelove and Witts criteria [6] and the Mayo score [7], allowed for a more objective assessment of the disease, and, while these are often used in clinical trials [8, 9], they are not yet validated.

This approach, directed at controlling and mitigating the consequences of inflammation, did not target the inflammatory activity itself. Some evidence exists that the correlation between symptoms and endoscopic findings in UC is better than for Crohn's disease (CD), with authors reporting a good correlation between endoscopy and stool frequency, and particularly rectal bleeding, of up to 0.76 (95% confidence interval [CI] 0.72–0.80] and 0.82 (95% CI 0.78–0.85), respectively. Notwithstanding, there is an imperfect correlation between symptoms and bowel inflammation [10], and more than half of all patients in clinical remission exhibit mucosal inflammation on endoscopy [11]. Conversely, there is a significant overlap between the clinical presentation of IBD and other conditions, such as irritable bowel syndrome (IBS) or infectious diarrhea [4], and some authors have reported UC patients on long-standing remission to present with IBS-like symptoms (abdominal pain, increased stool frequency) two to three times more often than controls [12], while others found increased stool frequency in up to 27% of patients with complete endoscopic and histological healing, suggesting a possible role of non-inflammatory functional bowel damage [13]. Finally, clinical remission while receiving placebo reached up to 15% in a systematic review of clinical trials [14], but there is mounting evidence that achieving clinical remission without mucosal healing (MH) does not associate with reduced rates of hospitalization or colectomy over the years [15, 16].

Other attractive options to monitor UC patients include the use of inflammatory markers, such as the serum markers C-reactive protein and erythrocyte sedimentation rate and the fecal marker calprotectin. The correlation between endoscopic activity and serum inflammatory markers is insufficient to warrant its broad use in UC [17]; for calprotectin, despite promising results [18–20], more studies are needed to clarify adequate surveillance strategies and cut-off levels before its broad implementation in clinical practice.

Mucosal inflammation is a key component of both UC and CD, but, unlike Crohn's disease, a transmural disease with both stricturing and penetrating phenotypes, disease activity is limited to the mucosa in UC [1, 2]. It is therefore no surprise that MH should prove an attractive target when approaching UC patients, regardless of the disease extent, inflammatory biomarkers, or clinical presentation. In the past decade, extensive evidence has been published advocating the importance of histological healing [21, 22] as it demonstrated excellent correlation with reduced risk of relapse [23] and hospitalization [24]. Some authors are now suggesting that histological healing could be included in the definition of MH in addition to the endoscopic findings [25].

Current treatment options for UC include aminosalicylates, such as sulfasalazine and mesalamine (5-aminosalicylic acid; 5-ASA) in both oral and rectal formulations, corticosteroids (including systemic corticosteroids such as prednisolone or hydrocortisone, and topical corticosteroids such as budesonide), thiopurines (azathioprine and 6-mercaptopurine), methotrexate, calcineurin inhibitors (ciclosporine and tacrolimus), anti-tumor necrosis factor (TNF)-α drugs (including infliximab, adalimumab, and golimumab), and, more recently, the anti-integrin drug vedolizumab [3, 26].

In this review, we aimed to provide an overview of the mechanisms involved in the balance of continuous mucosal injury and mucosal repair in UC, as well as the pathways through which different drug classes act upon the colonic mucosa towards reducing inflammation and promoting cell repair. Moreover, we aimed to cover the efficacy of the currently approved drugs for UC in achieving MH, and, ultimately, how MH impacts the course of the disease.

We performed a systematic search in the PubMed and Cochrane Library Central databases in order to identify relevant literature (the initial search was conducted in April 2016, and the final search was conducted in August 2016). No restrictions were applied to language or publication date. Keywords used included 'inflammatory bowel disease', 'ulcerative colitis', 'mucosal healing', 'endoscopic healing', and 'remission'. References of included articles were also searched.

2 Physiology and Pathology of Bowel Inflammation

2.1 Mechanisms Involved in Mucosal Injury

In order to fully grasp the scope of the importance of MH, as well as the mechanisms behind the therapeutic approach to UC, comprehending the physiopathological response involved in mucosal injury is required. An obvious concept of mucosal injury relates to visible lesions during endoscopy [1], but before ulcers and erosions become macroscopically apparent, several biochemical pathways are involved, including gap junction disruption at a molecular level, increased epithelial permeability, cellular apoptosis, mucosal infiltration of activated inflammatory and lymphocytic cells, villous and crypt architectural changes, and destruction [27]. This cascade is most likely initiated when a combination of bacterial, alimentary, and endogenous factors lead to mucosal cell damage and destruction [27], with resulting loss of mucosal integrity. The bowel mucosa acts as a barrier between the environmental antigens, including the microbiota, and the host immune system. After the breakdown of the mucosal barrier function, a translocation of antigens to the mucosal *lamina propria* occurs, leading to the activation of innate and adaptative immune response [27]. The mechanisms behind the epithelial cell damage are only partially unveiled, but several molecules have been found to play a role in this process: TNFα, a cytokine involved in a myriad of inflammatory processes, induces intestinal cell apoptosis [28]; reactive oxidants, such as superoxide and nitric oxide, induce and amplify mucosal injury [29]; and an excess of matrix metalloproteinases has been found in ulcerated bowel lesions [30].

2.2 Mechanisms and Drugs Involved in Mucosal Healing (MH)

The mechanisms involved in MH are just as complex as for mucosal injury, and include goblet cell repair to preserve an intact mucus layer [27], Paneth cell replenishment to sustain adequate antimicrobial function and allow healing of the epithelial wound [31], and multiple pathways resulting in the recruitment of molecules, such as transforming growth factor or intestinal trefoil factors, in order to close the epithelial gap and reseal the wounded mucosa [27].

Currently approved drugs for UC may act at one or more of the different stages of mucosal injury: pre-epithelial (intestinal mucosal layer, bacteria, alimentary antigens), epithelial, or post-epithelial (immune response, modulation of cytokines and growth factors) [27].

Both corticosteroids and aminosalicylates have been used for decades and are among the most commonly prescribed drugs for UC [3]. The mechanisms through which they reduce mucosal inflammation include controlling nuclear factor (NF)-κB expression (a molecule associated with microscopic tissue abnormalities in IBD) and inflammatory cytokines (directly modulating cell migration and proliferation of epithelial cell lines) [32–34]. In addition, aminosalicylates play a role on the suppression of the cyclooxygenase-2 gene [35].

Azathioprine and its metabolite 6-mercaptopurine are thiopurine immunomodulators and act primarily upon the immune system response by reducing inflammatory infiltrate in the bowel mucosa, inducing apoptosis and limiting cell proliferation, consequently arresting the inflammatory cycle [36].

Calcineurin inhibitors, such as cyclosporin and tacrolimus, reduce the TNF-secreting cells in the gut mucosa in addition to their effects in both T- and B-cell-mediated immunity [27].

Anti-TNFα drugs, such as infliximab, adalimumab, and golimumab, act at several steps of mucosal injury, restricting the inflammatory infiltrate and T-cell proliferation within the lamina propria [37], and downregulating the expression of metalloproteinases and proinflammatory molecules [37]. They also act on the regenerative process, restoring the protective capabilities of the mucosa by reinforcing intestinal permeability and mucosal secretion, activating fibroblasts, and maintaining epithelial regeneration [38].

Vedolizumab is a humanized anti-integrin antibody selective to its α4β7 heterodimer, and exerts its action in a rather specific mechanism by limiting both B- and T-cell lymphocyte fixation on the intestinal vascular endothelial cells and consequent migration to the lamina propria and tissue cells [26, 39].

Nevertheless, striking differences in the frequency, timing, and degree of MH may be found in different UC patients, even under similar pharmacological approaches, underlining the importance of several genetic, epigenetic, environmental and microbiotic factors in this process, a number of which are probably yet to be uncovered [27].

3 Current Definitions of MH

Endoscopically, active UC may present with various mucosal abnormalities, the most commonly observed being erythema, mucosal friability and bleeding, loss of vascular pattern, erosions, and ulcers [1]. The concept of MH in UC was first reported more than half a century ago in 1955 by Truelove and Witts [6], but where the line should be drawn in order to distinguish endoscopically active disease from

MH, and which lesions are most important when assessing UC clinical course and prognosis, remain controversial topics.

In part, heterogeneity stems from the presence of a large number of scores, each with its own set of variables, and several with adaptations and different cut-off points, resulting in over 20 different definitions of MH just in UC clinical trials. The endoscopic component of the clinical Mayo score, introduced in 1987, is currently the most used score in clinical practice [7]. It includes the variables erythema, loss of vascular pattern, friability, bleeding, erosions and ulcers, and ranges from 0 to 3—MH is classically considered to be a score of 0 (normal mucosa) or 1 (mucosal erythema, decreased vascular pattern, mild friability) [40]. The Mayo Endoscopic Score (MES) has several shortcomings, the most important being its low interobserver agreement [4], which, until now, has precluded its validation despite its widespread use and continuous modifications [8].

In 2007, the International Organization for the Study of Inflammatory Bowel Disease considered MH as the absence of friability, blood, erosions, and ulcers in all segments of the bowel mucosa [41], while erythema and loss of vascular pattern did not preclude the definition of MH. In line with this, most clinical trials in the anti-TNFα era adapted the MES by considering any friability as MES 2 and excluding it from the definition of MH [8, 42, 43].

However, some authors have recently reported significant differences in clinical outcomes, such as clinical relapse, hospitalization, and surgery rates, between patients with MES 0 and MES 1 [44–46], while others found a significant association between MES 0 and a higher likelihood of achieving histological healing [19]. The most recent ECCO guidelines consider endoscopic remission as MES $\leq$1, but complete MH as MES 0 [47].

The Baron score, developed in 1964, is another frequently employed score. In this score, the variable ulceration is absent and MH is defined as the absense of friability [48]. This score was further modified and employed in different configurations in clinical trials [49, 50] using markedly different cut-offs to categorize MH, but neither the original score nor the modified versions have been validated.

Other scores have been developed, such as the Rachmilewitz Endoscopic Index [51] and the St. Mark's Index [52], while some authors simply used isolated endoscopic findings to distinguish mucosal inflammatory activity from MH, such as the large Norwegian population-based study conducted by Froslie et al. [53].

More recently, the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) was introduced in clinical practice [54], and including bleeding, vascular pattern, and erosions/ulcers as variables. This score demonstrated excellent interobserver agreement [55] and a superior correlation with clinical outcomes, long-term prognosis, and mucosal improvement during therapy when compared with the Mayo score [56], but is only partially validated [55] and lacks defined cut-offs for severity of endoscopic disease activity and for MH.

Finally, to date, the Ulcerative Colitis Colonoscopic Index of Severity (UCCIS) is the only prospectively validated score [57], demonstrating good correlation with clinical markers and clinical activity, but it requires the expert evaluation of six different variables and no defined MH threshold has been defined. Table 1 summarizes the different scoring systems for UC, as well as the included variables and threshold for MH, when applicable.

In order to attenuate the negative influence of low interobserver agreement exhibited by most endoscopic scores, a concept of 'central reading' gained progressive relevance, where endoscopic video evaluation is performed off-site, by one or more experienced central readers [54, 58, 59]. Additionally, on-site reading may suffer from biases such as the willingness to include patients even when inclusion criteria may not be completely met [60]. While further studies are needed to confirm these advantages, promising evidence exists that central reading may improve adherence to the inclusion criteria [60], as well as to refine data interpretation, such as the correction of inadequately high placebo healing rates [61].

4 Achieving MH

4.1 Aminosalicylates

Of all the treatment options currently available for UC, the most prevalent is undoubtedly mesalamine [3]. Unlike CD, where aminosalicylates have little effect on clinical activity and do not induce MH, several authors have demonstrated their efficacy in achieving both clinical and mucosal remission in UC patients [62]. In a recent meta-analysis, including patients with mild to moderate UC, MH was achieved in 37% of patients taking oral mesalamine and 50.3% of patients taking rectal mesalamine, with no differences between formulations (granules vs. tablets or enemas vs. foam vs. suppositories) or delivery systems [63]. Other authors found no differences in efficacy between once, twice or three times daily administration of mesalamine [3], while a dose-dependent effect of mesalamine on MH was demonstrated in the pooled-analysis of the ASCEND 1 and 2 trials as mesalamine at a dosage of 4.8 g/day was significantly associated with a higher incidence of MH when compared with 2.4 g/day in patients with mild to moderate UC (80 vs. 68% at week 6;

Table 1 Ulcerative colitis endoscopic activity scoring systems

Score	Variables	Score range	Score for MH	Validated
Mayo endoscopic score (MES) [29]	Erythema	0–3	0–1 or 0[b]	No
	Vascular pattern			
	Friability[a]			
	Bleeding			
	Erosions and ulcers			
Baron Score [30]	Granularity	0–3	0–1[c]	No
	Erythema			
	Vascular pattern			
	Friability			
	Bleeding			
	Erosions and ulcers			
Rachmilewitz endoscopic index [33]	Granularity	0–12	0–4	No
	Vascular pattern			
	Bleeding			
	Mucosal damage (erosions, ulcers, exudate)			
St Mark's Index [34]	Friability	0–2	0	No
	Exudate			
	Bleeding			
Truelove and Witts [6]	Temporal evolution[d]	0–3	Not defined	No
Ulcerative colitis endoscopic index of severity (UCEIS) [36]	Vascular pattern	0–8	Not defined	Partially
	Bleeding			
	Erosions and ulcers			
Ulcerative colitis colonoscopic index of severity (UCCIS) [39]	Granularity	0–16	Not defined	Yes, prospectively
	Vascular pattern			
	Friability and Bleeding			
	Erosions and ulcers			
	Segmental and global assessment[e]			

MH mucosal healing

[a] In the modified Mayo Score, any friability scores as MES 2

[b] 0–1 is considered in most clinical trials; recent evidence points towards MES 0 as the most accurate representation of MH

[c] Any mucosal abnormality, except friability, is considered MH

[d] This score bases its assessment on comparison with previous observations, and lacks defined endoscopic descriptors

[e] UCCIS score implies complete observation of the colon, as well as both global and segmental assessment of the entire mucosa in a 4-point scale of severity

$p = 0.012$) [64]. In an elegantly designed prospective study by Meucci et al. [43], the combination of oral and topical mesalamine led to MH (corresponding to an MES ≤ 1) in 67% of patients. The combination therapy has been shown to improve MH compared with either oral or topical mesalamine alone in several other trials, with reported efficacy reaching up to 80% [65, 66]. The long-term efficacy of mesalamine was demonstrated in the recently published MOMENTUM trial [67] for MMX Mesalamine®, where MH was identified in up to 64% of patients with clinical response and 76% of those with clinical remission at 12 months after induction therapy.

4.2 Corticosteroids

In 1955, Truelove and Witts [6] reported that corticosteroids were shown to be capable of not only improving clinical symptoms but also inducing MH—endoscopic remission was observed in 30% of patients under treatment versus 10% of those receiving placebo ($p = 0.02$). Since

then, few studies have focused on the relationship between steroids and MH in UC, until a prospective study by Ardizzone et al. [49] demonstrated that up to 35% of patients achieve MH after just one corticosteroid course; however, long-term results are dismaying. Corticosteroids are currently considered to be able to induce, but not maintain, MH in UC patients [3, 40, 49].

Budesonide is a high-potency steroid with low systemic effects (compared with other steroids, budesonide undergoes significant first-pass metabolism), with a more favorable safety profile over systemic steroids. Because budesonide in its traditional oral formulation has limited efficacy in the colon [3], its administration has been largely limited to a foam rectal preparation, with limited efficacy in both clinical and endoscopic endpoints [3]. Recently, two strategies to enhance its efficacy have been developed. First, a Japanese multicenter, prospective study demonstrated a threefold significant increase in MH for patients treated with twice the standard dose of budesonide (46.6% for budenoside 2 mg twice daily vs. 23.6% for 2 mg once daily; odds ratio [OR] 3.024; $p < 0.001$) at week 6 of treatment [68], although at a cost of increased adverse events (53.6 vs. 30.9%; $p < 0.05$). Second, the development of MMX Budesonide®, a once-daily 9 mg oral budesonide with colon delivery formulation, resulted in its approval for use in mild to moderate UC [69]. A review of the currently available clinical trials found it to be significantly superior to placebo at achieving clinical remission plus MH (17.7 vs. 6.2%, $p < 0.001$; OR 3.3, 95% CI 1.7–6.4), but a low incidence of MH should be noted on both the treatment and placebo arms [70].

4.3 Immunomodulators

While thiopurines in monotherapy have long been associated with MH in CD [36], data in UC patients were, until recently, much scarcer. In a prospective, randomized trial, azathioprine induced MH in 58% of UC patients, compared with 21% in those receiving mesalamine (OR 5.26, 95% CI 1.59–18.1) [71]. Studies with longer follow-up, up to 2 years, have reported a similar incidence of long-term MH with azathioprine monotherapy, ranging from 37 to 57% [53, 72, 73]. In the UC SUCCESS randomized trial [74] for patients with moderate to severe UC, MH at week 16 was significantly less frequent when azathioprine was used in monotherapy (36.8%) than for infliximab monotherapy (54.5%; $p = 0.028$) or combination therapy (62.8%; $p < 0.001$). The pharmacokinetic and metabolite pathways involved in thiopurine mechanism of action and dose-dependent adverse events are complex [75]. Attempts to improve clinical response and reduce adverse effects in CD management, using an individualized approach by measuring circulating metabolite levels, have failed to unequivocally demonstrate an advantage over conventional weight-based dosage [76]. No such studies have been undertaken in UC patients.

Few studies exist regarding the use of methotrexate in UC patients. A Cochrane review failed to demonstrate an advantage over placebo for the maintenance of endoscopic or clinical remission in UC [77], while the more recent METEOR trial, employing higher doses of up to 25 μg/week in corticosteroid-dependent patients, did not show an increase in MH for patients receiving methotrexate (35 vs. 25% in the placebo arm; $p = 0.28$) [78].

Cyclosporin and tacrolimus have been used for corticosteroid-refractory acute severe UC. In a randomized controlled trial, 44% of these patients achieved MH [79]. However, the frequency and severity of adverse effects, including arterial hypertension, diabetes mellitus, hyperkalemia, and infections limit the chronic use of these drugs and they are often considered as a bridge to other immunosuppressive drugs, such as thiopurines [80].

4.4 Anti-Tumor Necrosis Factor-α Drugs

To date, anti-TNFα agents (infliximab, adalimumab, or golimumab) have shown the most robust evidence for efficacy in achieving MH among the approved drugs for UC [81]. Anti-TNFα drugs are usually reserved for patients with moderate to severe UC, often steroid refractory, and were approved following clinical trials performed in this population. In a network meta-analysis, anti-TNFα drugs were significantly more effective than placebo in achieving MH (relative risk [RR] 0.75, 95% CI 0.66–0.94; $p < 0.01$) [81].

In the combined analysis of the ACT1 and ACT2 trials in moderate to severe UC, 49.9% of patients taking infliximab achieved MH at week 54, compared with 21% taking placebo ($p < 0.05$). When considering MES 0, 33% of patients taking infliximab achieved this stricter definition of MH, more than twice as often as patients taking placebo (16%, $p < 0.05$) [8].

Regarding adalimumab, the ULTRA 1 trial failed to demonstrate improved efficacy compared with placebo for achieving MH at week 8 (47 vs. 41%; $p =$ non-significant) [82]. The ULTRA 2 trial, with a duration of 52 weeks, included both anti-TNFα-naive and anti-TNFα-experienced patients [83]. Patients taking adalimumab more frequently achieved MH than those taking placebo, both at week 8 (41 vs. 32%, $p = 0.032$) and week 52 (25 vs. 15%, $p = 0.009$). However, when stratified by prior anti-TNFα use, the superiority of adalimumab was only significant for naive patients (49 vs. 35%, $p = 0.014$, at week 8; and 31 vs. 19%, $p = 0.018$, at week 52) [83]. In a combined analysis of the ULTRA trials, after 4 years of follow-up more than 25% of patients with moderate to severe UC treated with adalimumab remained in MH [84].

The PURSUIT trial enrolled more than 1000 patients and evaluated the efficacy of golimumab for inducing and maintaining both clinical remission and MH [85, 86]. In this trial, golimumab was superior to placebo in achieving MH, both at the end of induction (44 vs. 29%, $p < 0.002$, at week 6) and following 1 year of maintenance treatment (42 vs. 27%, $p = 0.002$) [85, 86].

With regard to combination therapy, combining infliximab with a thiopurine (the UC SUCCESS trial) did not result in increased rates of MH when compared with infliximab alone when the endpoint MES <2 was considered (62.8 vs. 54.6%; $p = 0.295$), but a post hoc analysis identified a higher proportion of patients with MES 0 when combination therapy was used (29.5 vs. 11.7%; $p = 0.014$) [74].

Significant emphasis has recently been put on the pharmacokinetics of anti-TNFα drugs, particularly for their serum trough levels, as it has shown critical importance in order to achieve both clinical remission and MH [87, 88]. In fact, trough levels above 3–7 μg/mL for infliximab [87, 89, 90] and 5–8 μg/mL for adalimumab [88] were associated with a significantly increased likelihood for patients to achieve MH (OR 5.60, 95% CI 2.81–11.15 [91]), while an incremental gain in MH depending on anti-TNFα levels was recently demonstrated in a study by Ungar et al. [88]. These findings led to the suggestion that an MH therapeutic window may exist, within which MH is most likely to be achieved, while values above such a window will result in toxicity without further clinical benefit; the exact threshold is yet undetermined, and is likely to be influenced by individual factors, but highlights the growing importance of pharmacokinetics and pharmacodynamics in the management of IBD, as well as the advantages of a tailored approach to treatment. Finally, while golimumab serum levels were significantly associated with clinical response in the PURSUIT trial [85], there is as yet no published evidence regarding their relation with MH.

Anti-drug antibodies (ADAs) against anti-TNFα drugs are one of the most important variables in regulating the pharmacokinetics of anti-TNFα drugs; all anti-TNFα drugs have the potential for immunogenicity and ADA formation [92]. Once formed, ADAs bind anti-TNFα drugs, resulting in accelerated clearance and reduced half-life being extensively correlated with loss of clinical response and inability to achieve MH [89, 93]. An increased risk of ADA formation exists for patients with previou slow trough levels of anti-TNFα, episodic administration of anti-TNFα drugs, and previous ADA formation to another drug in this class [90, 92]. Current strategies employed to prevent their formation include increasing the dose and shortening the intervals of administration [80].

There is ample evidence that adding a thiopurine to an anti-TNFα drug significantly reduces ADA formation in CD, and, to a lesser extent, in UC [80], with improved anti-TNFα clearance and increased trough levels to within therapeutic range [87, 89, 94]. This reduction in ADA formation seems particularly beneficial during the first 12 months of anti-TNFα therapy [93], while the choice to maintain the thiopurine beyond this point should be weighed against the risks of long-term combination therapy, namely the increased risk of non-Hodgkin lymphoma [3]. Both anti-TNFα drugs and ADA concentrations are dependent on a number of other variables, including patient sex and body mass [95], albumin and C-reactive protein serum levels [96],circulating TNFα [80, 97], and even the severity of mucosal inflammation [80]. Currently, most evidence regarding ADAs is aimed at the post-induction treatment phase [88, 93], but earlier time points, allowing for detection of variability in anti-TNFα exposure and clearance, together with biomarkers and clinical assessment, could result in tailored induction regimens, optimizing both clinical and endoscopic response and potentially reducing adverse effects and costs.

4.5 Anti-Integrin Drugs

In the GEMINI trial, patients treated with vedolizumab achieved MH significantly more frequently than patients receiving placebo, both at week 6 (40.9 vs. 24.8%; $p < 0.001$) and week 52 (52 vs. 20%; $p < 0.001$), respectively [26]. Unfortunately, the few vedolizumab studies developed since this trial was published were limited to clinical assessment only, and further evidence is warranted to consolidate its capacity to induce MH in UC patients.

Table 2 summarizes the characteristics of the most important trials on the different drugs approved for UC, as well as their results for achieving MH. Current drugs with enough evidence for their association with MH in UC are salicylates, corticosteroids (induction only), calcineurin inhibitors (induction only) thiopurines, vedolizumab, and all approved anti-TNFα drugs.

Finally, treatment non-adherence is a key factor in both clinical response and MH, often overlooked in the clinical trials setting but recognized as an independent risk factor for persistent inflammatory activity by several authors [63].

However, a crucial point is the growing evidence regarding persistent clinical activity in patients where MH was achieved. Even in patients with partial clinical response, up to 35% presented with MES 0 during endoscopy. This finding highlights the overlap between IBD and IBS, and the limitations of the symptom-based assessment of disease activity [67, 98].

Table 2 Trials for approved drugs for UC

Drug	Trial	Year (published)	Inclusion criteria	Patients (*n*)	Control group	Design	Definition of MH	Timing of MH assessment	Incidence of MH
Mesalamine (4.8 g/day)	Pooled analysis of ASCEND 1 and 2 [64]	2011	Mild to moderate UC	391	Mesalamine 2.4 g/day	Double-blind	MES <2	Week 6	80 vs. 68%; $p = 0.012$
Azathioprine	Ardizzone et al. [71]	2006	Steroid-dependent UC	72	Mesalamine	Single-blind	Baron endoscopic score 0–1	Week 26	58 vs. 21% (OR = 5.26; 95% CI 1.59–18.1)
Methotrexate	METEOR [78]	2016	Steroid-dependent UC	111	Placebo	Double-blind	MES <2	Week 16	35 vs. 25%; $p = 0.28$
Infliximab	Pooled analysis of ACT 1 and ACT 2 [8]	2011	Moderate to severe UC, naïve to anti-TNFα drugs	728	Placebo	Double-blind	mMES <2	Week 8	MH: 61 vs. 33% ($p < 0.009$)
									MES 0: 25 vs. 8% ($p < 0.009$)
								Week 54	MH: 50 vs. 21% ($p < 0.009$)
									MES 0: 33 vs. 16% ($p < 0.009$)
Adalimumab	ULTRA 1 [82]	2011	Moderate to severe UC, naïve to anti-TNFα drugs	390	Placebo	Double-blind	mMES <2	Week 8	47 vs. 41%; $p =$ NS
Adalimumab	ULTRA 2 [83]	2012	Moderate to severe UC	494	Placebo	Double-blind[a]	mMES <2	Week 8	Total: 41 vs. 32%; $p = 0.032$
			Naïve to anti-TNFα drugs or discontinued for >8 weeks						Anti-TNFα naïve: 49 vs. 35%; $p = 0.014$
									Prior Anti-TNFα: 29 vs. 27%; $p = 0.773$
								Week 52	Total: 25 vs. 15%; $p = 0.009$
									Anti-TNFα naïve: 31 vs. 19%; $p = 0.018$
									Prior Anti-TNFα: 15 vs. 10%; $p = 0.250$
Golimumab	PURSUIT [85, 86]	2014	Moderate to severe UC, naïve to anti-TNFα drugs	1065	Placebo	Double-blind	mMES <2	Week 6	44 vs. 29%; $p < 0.002$
								Week 54	42 vs. 27%; $p = 0.002$
Vedolizumab	GEMINI [26]	2013	Moderate to severe UC	895	Placebo	Double-blind	mMES <2	Week 6	41 vs. 25%; $p < 0.001$
			Naïve to anti-TNFα drugs or discontinued for >60 days					Week 52	52 vs. 20%; $p < 0.001$
IFX (combo/monotherapy)	UC-Success [74]	2014	Moderate to severe UC	231	AZA	Double-blind, double dummy	mMES <2	Week 16	IFX + AZA > AZA (62.8 vs. 36.8%; $p = 0.001$)
									IFX > AZA (54.5 vs. 36.8%; $p = 0.028$)
									IFX + AZA = IFX (62.8 vs. 54.5%; $p = 0.295$)

MES Mayo Endoscopic Score, *mMES* modified Mayo Endoscopic Score (any friability is considered MES 2), *MH* mucosal healing, *IFX* infliximab, *AZA* azathioprine, *UC* ulcerative colitis, *TNF* tumor necrosis factor, *OR* odds ratio, *CI* confidence interval, *NS* non-significant

[a] Crossover of non-responders to open-label adalimumab was allowed starting on week 12

5 Prognostic Relevance of MH

The importance of MH has been known since 1966, when Wright and Truelove [99] performed serial biopsies on UC patients and concluded that patients in MH were more frequently in clinical remission after 1 year (40 vs. 18%). Since then, a number of authors and clinical trials have reported on the various outcomes of UC and the influence of several intervening factors, particularly MH.

In the pre anti-TNFα era, a large population-based study in Norway identified a reduced 5-year risk of colectomy in patients achieving MH (2 vs. 7%; RR 0.22, 95% CI 0.06–0.79) [53], independently of the drugs used to this end. Another study in a group of mild to moderate UC patients, performed by Meucci et al. [43], demonstrated that only 23% of patients in clinical remission and MES ≤ 1 presented with clinical relapse within 12 months, compared with 80% of those achieving clinical remission only. The study by Ardizzone et al., including newly diagnosed UC patients needing steroids, demonstrated a significant decrease in both hospitalization (hazard ratio [HR] 3.6, 95% CI 1.56–8.48) and surgery (HR 8.40, 95% CI 1.23–55.19) rates over 5 years for patients within a stringent definition of MH (Baron Score = 0) [49].

In the combined post hoc analysis of the ACT1 and ACT2 trials, MH after the infliximab induction phase (week 8) was significantly associated with long-term corticosteroid-free remission ($p < 0.001$) and a decreased risk of colectomy (5 vs. 15%; $p < 0.001$) at both week 30 and week 54. Additionally, up to 77% of patients in MH at week 8 were still in MH at week 54 [8]. Similarly, a prospective Italian study showed that patients in MH at 3 months of treatment for moderate to severe UC had less clinical relapse at 15 months (27.5 vs. 73.9%) [100], while a French multicenter study found striking differences in long-term colectomy rates between patients with MH (3%) and without MH (39%). In multivariate analysis, MH was indeed the only variable associated with colectomy-free survival (OR 18.01, 95% CI 1.58–204.92). Interestingly, the authors also demonstrated a significantly higher risk of cumulative infliximab failure for up to 4 years after treatment initiation if MH was not present at the index endoscopic evaluation (OR 3.23, 95% CI 1.48–7.0), suggesting that MH could play an important protective role against secondary anti-TNFα failure.

A common concern in patients with longstanding UC is the increased risk of dysplasia and colorectal cancer, which is thought to be consequential to persistent colonic inflammation [47]. Several authors have reported on an increased risk of dysplasia and progression to colorectal cancer in patients with endoscopically active disease when compared with those presenting with MH [101, 102], while others have demonstrated a normalization of the risk to that of a health individual when complete MH was achieved [103]. In a 2005 meta-analysis, the use of mesalamine was further associated with a significant decrease in the risk of colorectal cancer (OR 0.51, 95% CI 0.37–0.69) [104], but whether this improved outcome is solely related to the decrease in epithelial inflammation or complemented by anticarcinogenic properties of the drug has not yet been elucidated.

It should be noted that all drug clinical trials to date used a broader definition of MH, including patients with mild erythema or loss of vascular pattern (corresponding to modified MES 1). This option resulted in striking differences when evaluating drug efficacy. For instance, if the ASCEND trial results were adapted to exclude MES 1, and consider MH as MES 0, only 32% of patients taking mesalamine 4.8 g/day would be in MH, not 80% as was reported in the trial [64]. Because of competing commercial interests, new drugs tend to use the same endpoints as those previously used, easing comparison and underscoring improved results.

5.1 Mayo Endoscopic Score (MES) 0 Versus MES 1

Recently, various authors have reported on different outcomes in patients with MES 0 (no mucosal abnormalities) and MES 1 (mild erythema or decreased vascular pattern), while others now strictly define MH as an endoscopically normal mucosa.

In the subgroup analysis of the ACT1 and 2 trials, patients with MES 0 were significantly more often in corticosteroid-free remission after 1 year of follow-up than patients with MES 1 (73 vs. 47%; $p < 0.001$), while no differences were found in the colectomy rate [8]. Two Japanese studies with a 5-year follow-up (Yokoyama et al. [105] and Nakarai et al. [46]) were also among the earliest to report on different outcomes for complete MH. The former demonstrated a correlation between MES at baseline and risk of clinical relapse during follow-up, and a significant difference in sustained remission between MES 0 (78%) and MES 1 (40%; $p < 0.001$). Similarly, the latter found patients with MES 1 presented with an increased risk of clinical relapse when compared with MES 0 (HR 8.17, 95% CI 4.19–17.96), but also an increased risk of hospitalization (HR 10.48, 95% CI 1.90–195.22) [46]. Again, neither study demonstrated a difference in colectomy rates, suggesting perhaps that while MES 1 is associated with adverse outcomes, such inflammation is probably not as severe as to increase the risk of colectomy or to increase it in a tenuous manner. Adequately powered trials may be needed to enlighten this subject.

A prospective study by Barreiro-de Acosta et al., including patients in clinical remission with either MES 1 or MES 0 during endoscopy studies, reported a relapse rate of 26.2% after 12 months of follow-up [45]. The risk of relapse was significantly higher in patients with MES 1 (41.0 vs. 19.3%; $p < 0.01$), as confirmed in a Kaplan–Meier survival analysis (Chi-square 13.46; $p < 0.001$). This effect was independently significant for all three extents of disease. The latest evidence towards the significance of complete MH comes from a Portuguese study [44] in which patients with MES 1 were at increased risk of relapse during follow-up (27.3 vs. 11.5%; $p = 0.022$) and adverse outcomes, including the need for corticosteroids and hospitalization (13.0 vs. 3.3%; $p = 0.044$). In the subgroup analysis of disease extent, patients with left-sided and extensive colitis and MES 1 were at increased risk of relapse, but not in cases of proctitis. In both studies, MES 0 was the only variable associated with clinical relapse in multivariate analysis (OR 6.27, 95% CI 2.73–14.40, and OR 2.89, 95% CI 1.14–7.39, respectively [44, 45]). While previous studies showed no differences in colectomy rates between MES 0 and MES 1, these recent works report no colectomy at all, reflecting a progressive paradigm shift in UC as the treat-to-target approach towards MH in UC patients becomes the norm, and more severe consequences of the disease tend to be seldom observed. The summarized findings of these studies comparing the outcomes between MES 0 and MES 1 are included in Table 3.

6 Current and Future Perspectives

6.1 Advanced Endoscopic Imaging

As the tide turns and more clinicians turn their aims towards complete MH, the knowledge and technology advances towards more accurate and detailed observation during endoscopy. Recently, advanced imaging techniques, such as high-definition colonoscopy, magnifying endoscopy, and virtual chromoendoscopy, have been suggested as a complement to white-light colonoscopy. Virtual chromoendoscopy has resulted in a significant increase in characterization of both severity and extent of mucosal inflammation in UC patients ($p < 0.001$), with no increase in procedure duration in a randomized controlled trial [106], and, in a multicenter study, was not only more sensitive than white light in the detection of mild endoscopic changes but also correlated more accurately with histological activity [107].

6.2 Histological Healing

Histological healing has long been reported as an important endpoint for UC patients, and some authors are now suggesting that histology could combine with endoscopy, or even supersede it, as the most adequate method for assessment of MH in UC patients.

As early as 1991, histological activity has been associated with an increased risk of relapse at 12 months, when Riley et al., in a study of 82 patients, found significantly higher disease relapse rates for UC patients with either of the following histological markers: acute inflammatory cell infiltrate, crypt abscesses, mucin depletion, and breaches in the surface epithelium [108]. More recently, histological healing was additionally associated with a reduced risk of hospitalization and colectomy [109, 110] for as long as 6 years of follow-up [24]. Basal plasmocytosis, in particular, was identified as a marker of histological activity, present in up to 21% of patients despite MH [4], and significantly associated with an increased risk of disease relapse [22]. Later, the development of the Geboes score and the Riley score have allowed objective measurement of histological activity, and both demonstrate excellent interobserver agreement [18, 111]. Many other scoring systems followed, and as many as 20 have been described to date [25, 112, 113], including the recently validated Robarts histopathology index [112] and the Nancy score [113].

There is some evidence that significant histological activity may be present in up to 24–40% of UC patients with endoscopic findings compatible with MH [19, 22, 24, 110]. However, it should be noted that complete MH (MES 0) was significantly associated with a lower incidence of histological activity when compared with MES 1 (7 vs. 52%; $p < 0.001$) [19], and was reported to accurately reflect normal histology on biopsies [13, 114].

Currently, the use of histological healing as an endpoint is hindered by the absence of prospective studies evaluating the impact of current drugs, particularly anti-TNFα agents, in the process of histological healing, as well as by insufficient data regarding long-term outcomes such as disease progression, hospitalization, and surgery [21, 41].

7 Conclusions

UC is a chronic inflammatory disease with severe consequences, including the need for hospitalization and colectomy and the increased long-term risk of colorectal cancer.

Most of the currently approved drugs for UC, including the widely employed aminosalicylates, thiopurines such as azathioprine, vedolizumab and, in particular anti-TNFα drugs, have shown to be able to achieve and maintain MH in a large number of patients, and significantly more often than placebo.

MH has been significantly associated with improved outcomes in UC patients, and established itself as a

Table 3 Studies comparing outcomes between MES 1 and MES 0

Authors	Country, year of publication	Patients (*n*)	Follow-up	Main results
Colombel et al. [8]	International Multicenter, 2011	147[a]	12 months	Significantly higher clinical relapse in patients with MES 1 compared with MES 0 73 vs. 47%; $p < 0.001$ No differences in colectomy rates between MES 0 and MES 1 5 vs. 5%; $p =$ NS
Yokoyama et al. [105]	Japan, 2013	38	5 years	Significantly higher clinical relapse in patients with MES 1 compared with MES 0 60 vs. 22%; $p < 0.001$ No differences in colectomy rates between MES 0 and MES 1 Data not shown
Nakarai et al. [46]	Japan, 2014	183	5 years	Significantly higher clinical relapse in patients with MES 1 compared with MES 0 HR 8.17, 95% CI 4.19–17.96; $p < 0.001$ Increased risk of hospitalization in patients with MES 1 HR 10.48, 95% CI 1.90–195.22; $p = 0.0044$ No differences in colectomy rates between MES 0 and MES 1 Data not shown
Barreiro-de-Acosta et al. [45]	Spain, 2015	187	12 months	Significantly higher clinical relapse in patients with MES 1 compared with MES 0 41.0 vs. 19.3%; $p < 0.01$ In the subgroup analysis, MES 1 was associated with increased relapse in the three extents of the disease: Proctitis—25 vs. 5%; $p = 0.04$ Left-sided colitis—48 vs. 14%; $p < 0.01$ Extensive colitis—38 vs. 7%; $p < 0.02$ No colectomy during follow-up
Boal Carvalho et al. [44]	Portugal, 2015	138	12 months	Significantly higher clinical relapse in patients with MES 1 compared with MES 0 27.3 vs. 11.5%; $p = 0.022$ In the subgroup analysis, MES 1 was associated with increased relapse in left-sided and extensive colitis, but not proctitis Proctitis—25 vs. 12%; $p =$ NS Left-sided/extensive colitis—29.7 vs. 11.1%; $p = 0.049$ Increased risk of hospitalization/need for corticosteroids in patients with MES 1 13.0 vs. 3.3%; $p = 0.044$ No colectomy during follow-up

MES Mayo Endoscopic Score, *HR* hazard ratio, *NS* non-significant, *CI* confidence interval

[a] Total number of patients in the ACT1 and 2 trials = 728; only 147 were included in the subanalysis of patients with MES 0 or MES 1 at week 8

crucial endpoint in the management of the disease in both retrospective and prospective studies. Nevertheless, while clinical practice is currently adapting to the available evidence, and switching from a symptom-based approach towards endoscopic-based management, so too is the definition of mucosa healing in constant adjustment.

Recent evidence has shed light on the importance of not just partial but complete MH as a preferred goal while planning patient treatment. Histological healing may one day be the ultimate endpoint for UC. For achieving these ambitious goals, a perfect interaction is needed between increasingly accurate endoscopic, and even histological, assessment of the disease and prompt and adequate

treatment with effective drugs, capable not only of controlling the symptoms but muting the inflammation itself.

Compliance with Ethical Standards

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